

PATENT SPECIFICATION

NO DRAWINGS

890,638



Date of Application and filing Complete Specification: June 11, 1958.

No. 18710/58.

Application made in United States of America on June 11, 1957.

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Index at acceptance:—Class 81(1), B1(B3: C: D: L: S), B2(B3: C: D: L: S).

International Classification:—A61k.

COMPLETE SPECIFICATION

Compositions for Combating Retinitis Pigmentosa

We, ALBERT B. CHATZINOFF, of 194—10C 64 Circle, Fresh Meadows, Long Island, New York, United States of America, WILLIAM C. MENDE, of Old Amwell Road, Neshanic, New Jersey, United States of America, NATHAN MILLMAN, Bayberry Road, R.D. # 2, Somerville, New Jersey, United States of America, and WILLIAM OROSHNIK, of 1136 Dorsey Place, Plainfield, New Jersey, United States of America, all citizens of the United States of America, do hereby declare the invention.

the progress of the disease may be halted. The role of vitamin A and its aldehyde, retinene, in vision has been very thoroughly explored. Our knowledge of this process may be summarized as follows:

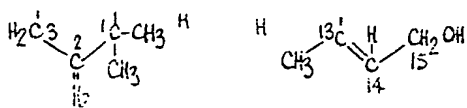
Vitamin A from the blood stream enters the retina. There it is oxidized by an enzyme system to retinene, and stereoisomerized to neoretinene b. In the absence of light, the neoretinene b is continuously removed by combination with the protein opsin. The com-

SPECIFICATION NO. 890,638

By a direction given under Section 17 (1) of the Patents Act 1949 this application proceeded in the name of Ortho Pharmaceutical Corporation, a corporation organised and existing under the laws of the State of New Jersey, United States of America, of Raritan, New Jersey, United States of America.

THE PATENT OFFICE,

DS 65291/1(2)/R.109 200 6/62 PL



or an ester of this isomer, in a pharmaceutical carrier.

Retinitis pigmentosa is a degenerative disease of the eye which appears in certain individuals who may have a genetic predisposition to it. It manifests itself in the gradual deterioration of the photosensitive cells in the eye with an accompanying deposition of pigment. The course of the disease may take place over a period of 10 to 20 years but in all cases severe impairment of vision results. Prior to the present invention, no therapy was known for it. We have now discovered that if the 11-cis isomer of vitamin A is administered orally, by injection, or rectally, [P-]

evidence indicates that 11-cis vitamin A may be oxidized to 11-cis retinene (neoretinene b) in the eye and that a continuous supply of 11-cis vitamin A to the eye can effectively correct the inability of the eye to convert retinene to neoretinene b. Thus, sub-minimal doses of the 11-cis isomer of vitamin A will maintain a healthy eye condition. On the other hand, retinal degeneration occurs when an equal (subminimal) amount of normal vitamin A is administered orally.

This invention embraces the use of the 11-cis isomer of vitamin A in various forms, for example, as such, or in the form of its esters, of which the acetate and palmitate are illustrative.

It has been found that the aforesaid 11-cis isomer has unexpected and unobvious properties of great value in combating retinitis pigmentosa. Insofar as is known, the physio-

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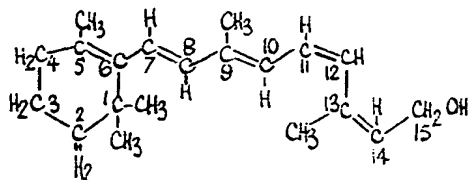
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COMPLETE SPECIFICATION

Compositions for Combating Retinitis Pigmentosa

We, ALBERT B. CHATZINOFF, of 194—10C 64 Circle, Fresh Meadows, Long Island, New York, United States of America, WILLIAM C. MENDE, of Old Amwell Road, Neshanic, New Jersey, United States of America, NATHAN MILLMAN, Bayberry Road, R.D. # 2, Somerville, New Jersey, United States of America, and WILLIAM OROSHNIK, of 1136 Dorsey Place, Plainfield, New Jersey, United States of America, all citizens of the United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with compositions useful in combating retinitis pigmentosa. More particularly, this invention relates to therapeutic compositions for combating retinitis pigmentosa, which comprise the 11-*cis* isomer of vitamin A having the structural formula:



or an ester of this isomer, in a pharmaceutical carrier.

Retinitis pigmentosa is a degenerative disease of the eye which appears in certain individuals who may have a genetic predisposition to it. It manifests itself in the gradual deterioration of the photosensitive cells in the eye with an accompanying deposition of pigment. The course of the disease may take place over a period of 10 to 20 years but in all cases severe impairment of vision results. Prior to the present invention, no therapy was known for it. We have now discovered that if the 11-*cis* isomer of vitamin A is administered orally, by injection, or rectally, [P-]

the progress of the disease may be halted. The role of vitamin A and its aldehyde, retinene, in vision has been very thoroughly explored. Our knowledge of this process may be summarized as follows:

Vitamin A from the blood stream enters the retina. There it is oxidized by an enzyme system to retinene, and stereoisomerized to neoretinene b. In the absence of light, the neoretinene b is continuously removed by combination with the protein opsin. The compound formed between neoretinene b and opsin is called rhodopsin. On contact with light the rhodopsin is immediately broken down to retinene and opsin, or in other words, is bleached. The released retinene re-enters the equilibrium with vitamin A and any excess of the latter that may occur as a consequence then goes back to the blood stream.

While the present invention is not to be limited to any particular theory of operation it seems likely that retinitis pigmentosa may be caused by the inability of the individual to convert the naturally occurring all *trans* retinene into the 11-*cis* isomer (neoretinene b) in sufficient quantities for the maintenance of a healthy metabolic condition in the eye. Our evidence indicates that 11-*cis* vitamin A may be oxidized to 11-*cis* retinene (neoretinene b) in the eye and that a continuous supply of 11-*cis* vitamin A to the eye can effectively correct the inability of the eye to convert retinene to neoretinene b. Thus, sub-minimal doses of the 11-*cis* isomer of vitamin A will maintain a healthy eye condition. On the other hand, retinal degeneration occurs when an equal (subminimal) amount of normal vitamin A is administered orally.

This invention embraces the use of the 11-*cis* isomer of vitamin A in various forms, for example, as such, or in the form of its esters, of which the acetate and palmitate are illustrative.

It has been found that the aforesaid 11-*cis* isomer has unexpected and unobvious properties of great value in combating retinitis pigmentosa. Insofar as is known, the physio-

logical properties of this isomer have not heretofore been investigated, nor has the compound been applied for therapeutic purposes.

Not only is the compound effective on administration by the oral route, but it is also effective when administered parenterally, for example, subcutaneously or intraperitoneally. The orally tolerated dose in humans is from 100 to about 150,000 Units. One milligram of the 11-*cis* isomer of vitamin A is equivalent to approximately 750 Units according to the U.S.P. growth method of assay. (See U.S.P. XIV, pages 789—792).

The percentage of active ingredient in the

	Adsorbent	1% — 60%
	Filler	40% — 90%
	Lubricant	0.5% — 10%
30	11- <i>cis</i> Isomer	100 — 50,000 Units

In making tablets, the vitamin A isomer must be adsorbed onto an inert adsorbent, such as kaolin, fuller's earth, magnesium oxide, calcium carbonate or starch.

The fillers are those generally used in the manufacture of tablets, such as lactose, dextrose, sucrose or mixtures of sugars.

Lubricating agents prevent sticking and binding of the powder mass in the dies and on the punches of the tableting machine. Those generally used are, for example, magnesium stearate, talc, calcium stearate or mineral oil.

Compressed or sugar-coated tablets disintegrate in the stomach. If it is desirable to circumvent the stomach and have the active ingredient released in the intestines, the compressed tablets may be enteric coated with, for example, shellac, salol (phenyl salicylate), cellulose acetate phthalate or mastic.

The following examples will illustrate specific formulas that may, however, be varied or modified to a considerable extent:

EXAMPLE I

1.	Calcium carbonate	0.01 Gm.
2.	11- <i>cis</i> isomer	100 Units
3.	lactose, q.s.	0.50 Gm.
4.	magnesium stearate	0.01 Gm.

Adsorb the 11-*cis* isomer on the calcium carbonate, add the lactose and granulate according to the art with starch paste. Dry, add the magnesium stearate, mix and compress into tablets. These tablets may be left uncoated, coated with sugar or enteric coated according to the art. Enteric coated tablets usually have a sugar coating over the enteric coating.

EXAMPLE II

1.	kaolin	0.200 Gm.
2.	11- <i>cis</i> isomer	50,000 Units
3.	lactose, q.s.	0.500 Gm.
4.	sucrose	0.100 Gm.
5.	calcium stearate	0.02 Gm.

compositions of the present invention may be varied. It is necessary that the 11-*cis* isomer of vitamin A or its ester constitute a proportion such that a suitable dosage will be obtained. Obviously several unit dosage forms may be administered at or about the same time. It is preferred to use not less than 1% by weight of the active isomer since activity decreases with concentration of the agent. The concentration of the isomer may be 10% or 25% or even a greater proportion. For example, in preparing tablets the following ranges are particularly useful:

Adsorb the 11-*cis* isomer on the kaolin, add the lactose and sucrose and granulate according to the art with gelatin solution. Dry, add the calcium stearate, mix and compress into tablets. These tablets may be left uncoated, sugar coated, or enteric coated.

The 11-*cis* isomer of vitamin A may be mixed with vitamin A in proportions of 1:100 to 100:1, although the proportion of 11-*cis* isomer may be greater.

EXAMPLE III

1.	fuller's earth	0.150 Gm.
2.	11- <i>cis</i> isomer	50,000 Units
3.	vitamin A	2,000 Units
4.	lactose, q.s.	0.500 Gm.
5.	talc	0.05 Gm.

Adsorb the 11-*cis* isomer and the vitamin A on the fuller's earth, add the lactose and granulate with starch paste. Dry, add the talc, mix and compress into tablets. These tablets may be left uncoated, sugar coated or enteric coated.

EXAMPLE IV

1.	Starch	0.20 Gm.
2.	11- <i>cis</i> isomer	5,000 Units
3.	vitamin A	25,000 Units
4.	lactose, q.s.	0.50 Gm.
5.	sucrose	0.10 Gm.
6.	magnesium stearate	0.01 Gm.

Adsorb the 11-*cis* isomer and the vitamin A on the starch, add the lactose and sucrose and granulate with acacia solution. Dry, add the magnesium stearate, mix and compress into tablets. These tablets may be enteric coated, sugar coated or left uncoated.

Hard gelatin capsule formulations differ from tablet formulations in that fillers are often not required and the powder mass need not be granulated. A decided advantage of this dosage form is that more adsorbent may be used for liquid active ingredients.

EXAMPLE V

Hard gelatin capsules may be enteric coated according to the art using the same enteric coating materials as for tablets.

- | | | |
|---|--------------------------|--------------|
| 5 | 1. kaolin | 0.30 Gm. |
| | 2. 11- <i>cis</i> isomer | 50,000 Units |
| | 3. magnesium stearate | 0.01 Gm. |

10 Adsorb the 11-*cis* isomer on the kaolin, add the magnesium stearate, mix and fill into capsules. These may or may not be enteric coated.

EXAMPLE VI

- | | | |
|----|--------------------------|-------------|
| | 1. Calcium carbonate | 0.20 Gm. |
| | 2. 11- <i>cis</i> isomer | 1,000 Units |
| 15 | 3. calcium stearate | 0.10 Gm. |

Adsorb the 11-*cis* isomer on the calcium carbonate, add the calcium stearate, mix and fill into capsules. These capsules may be enteric coated according to the art.

EXAMPLE VII

- | | | |
|----|--------------------------|--------------|
| 20 | 1. fuller's earth | 0.25 Gm. |
| | 2. 11- <i>cis</i> isomer | 25,000 Units |
| | 3. vitamin A | 10,000 Units |
| | 4. talc | 0.02 Gm. |

25 Adsorb the 11-*cis* isomer and the vitamin A on the fuller's earth, add the talc, mix and fill into capsules.

30 Concentrations of 100 to 50,000 Units of 11-*cis* isomer may be incorporated into standard vitamin preparations such as "U.S.P. Decavitamin Capsules."

Soft gelatin capsules are used as dosage forms for oily liquids. If an active ingredient is oil soluble, this becomes a very desirable form to dispense individual doses. These capsules are more convenient than measuring a dose of oil solution by drop, cc. or teaspoonful. Antioxidants are generally included in these oil solutions to prevent the oxidation of the active ingredients during the shelf-life of the product. Antioxidants, such as α -tocopherol, α -tocopherol acetate, *nor*-dihydroguaiaretic acid or "Ionol" (Registered Trade Mark) (2,6-di-tert.-butyl-4-methylphenol) may be used.

45 Soft gelatin capsules may be enteric coated according to the art using the enteric coating materials shown for tablets.

EXAMPLE VIII

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|----|--------------------------|--------------|
| | 1. corn oil | 0.200 cc. |
| 50 | 2. α -tocopherol | 0.001 Gm. |
| | 3. 11- <i>cis</i> isomer | 15,000 Units |

Dissolve the 11-*cis* isomer and the α -tocopherol in the corn oil, mix and fill into soft gelatin capsules. Enteric coat if desired.

EXAMPLE IX.

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|----|-------------------------------------|--------------|
| 55 | 1. sesame oil | 0.250 cc. |
| | 2. nordihydroguaiaretic acid | 0.001 Gm. |
| | 3. 11- <i>cis</i> isomer | 20,000 Units |
| 60 | Formulate as in Example VIII above. | |

EXAMPLE X

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|------------------------------------|--------------|----|
| 1. peanut oil | 0.400 cc. | |
| 2. "Ionol" (registered Trade Mark) | 0.001 Gm. | |
| 3. 11- <i>cis</i> isomer | 500 Units | 65 |
| 4. vitamin A | 25,000 Units | |

Dissolve the 11-*cis* isomer, the "Ionol" and the vitamin A in the peanut oil, mix and fill into soft gelatin capsules. Enteric coat if desired.

70 11-*cis* isomer in concentrations of 100 to 50,000 Units may be included in multivitamin preparations containing a mixture of vitamins such as are in U.S.P. Decavitamin Tablets and incorporated in oil and filled into soft gelatin capsules. These capsules may be enteric coated if desired.

The 11-*cis* isomer of vitamin A and its esters may also be added to liquid vitamin A preparations such as OLEUM PROCO-MORPHUM (a liquid vitamin A product sold by the Mead Johnson Co.).

80 It is well known that substances are absorbed from the rectum, so that rectal suppositories often provide a desirable form of therapeutic vehicle.

The 11-*cis* isomer may be incorporated into such preparations in concentrations of 100 to 50,000 Units—with or without vitamin A or other vitamins.

EXAMPLE XI.

- | | | |
|--------------------------|--------------|--|
| 1. cocoa butter, q.s. | 2 Gm. | |
| 2. 11- <i>cis</i> isomer | 40,000 Units | |

95 Dissolve the 11-*cis* isomer in the cocoa butter and mould into suppositories.

EXAMPLE XII

- | | | |
|------------------------------|--------------|-----|
| 1. Polyethylene glycol, 400 | 0.50 Gm. | |
| 2. polyethylene glycol, 5000 | 1.50 Gm. | 100 |
| 3. 11- <i>cis</i> isomer | 30,000 Units | |

Dissolve the 11-*cis* isomer in the two polyethylene glycols and mould into suppositories.

EXAMPLE XIII

- | | | |
|--------------------------|--------------|-----|
| 1. Cocoa butter, q.s. | 2.0 Gm. | |
| 2. beeswax | 0.01 Gm. | |
| 3. 11- <i>cis</i> isomer | 100 Units | |
| 4. vitamin A | 10,000 Units | 110 |

Dissolve the beeswax in the cocoa butter, add the 11-*cis* isomer and the vitamin A, mix and mould into suppositories. Oils, oily solutions and aqueous dispersions can be administered by intramuscular and subcutaneous injection. The speed of absorption of these injections may be modified by the addition of, for example, procaine.

EXAMPLE XIV

- | | | |
|--|--------------|-----|
| 1. sesame oil, q.s. | 1.0 cc. | 120 |
| 2. α -tocopherol | 0.001 Gm. | |
| 3. 11- <i>cis</i> isomer | 50,000 Units | |
| Dissolve the 11- <i>cis</i> isomer and the α -tocopherol in the sesame oil, and fill into ampoules. | | |
| | | 125 |

EXAMPLE XV

1. "Tween" 80 (registered Trade Mark) 0.01 Gm.
2. 11-*cis* isomer 20,000 Units
3. Ascorbic acid 0.01 Gm.
4. water for injection, qs. 1.0 cc.

Dissolve the 11-*cis* isomer in the "Tween" 80 (R.T.M.) and the ascorbic acid in the water, mix and fill into ampoules.

- 10 The following examples illustrate formulations that may be injected intravenously.

EXAMPLE XVI

1. lecithin (highly purified) 0.05 Gm.
2. 11-*cis* isomer 10,000 Units
3. sodium ascorbate 0.001 Gm.
4. water for injection, q.s. 1.0 cc.

Dissolve the 11-*cis* isomer in the lecithin and the sodium ascorbate in the water and fill into ampoules.

EXAMPLE XVII

- 20 1. Sucrose monostearate 0.05 Gm.
2. 11-*cis* isomer 5,000 Units
3. α -tocopherol acetate 0.001 Gm.
4. water for injection, q.s. 1.0 cc.

- 25 Dissolve the 11-*cis* isomer in the sucrose monostearate, add the α -tocopherol acetate and water, mix and fill into ampoules.

WHAT WE CLAIM IS:—

- 30 1. A therapeutic composition for combating retinitis pigmentosa comprising the 11-*cis* isomer of vitamin A in a pharmaceutical carrier.
2. A composition according to claim 1, wherein there is additionally present vitamin A, the 11-*cis* isomer being present in the amount of at least 1 unit for each 100 unit of vitamin A.
3. A composition according to claim 2, wherein the ratio of the 11-*cis* isomer to vitamin A is in the range of 1:100 to 100:1.
- 40 4. A composition according to any of claims 1 to 3, wherein there is additionally present, in the case where the carrier is a solid,

a binder and a lubricant.

5. A composition according to claim 4, wherein the composition is in dosage unit form for oral administration and is provided with an enteric layer of a substance which is substantially insoluble in acidic stomach secretions but soluble in alkaline intestinal fluids.

6. A composition according to claim 5, wherein the enteric layer is composed of phenyl salicylate.

7. A composition according to any of claims 4 to 6, wherein the solid carrier is calcium carbonate, the binder is lactose and the lubricant is magnesium stearate.

8. A composition according to any of claims 1 to 4, wherein the composition is in dosage unit form in sealed gelatin capsules.

9. A composition according to any of claims 1 to 3, which comprises not less than 1% by weight of the 11-*cis* isomer of vitamin A and a sterile parenteral water diluent.

10. A composition according to any of claims 1 to 3, which comprises not less than 1% by weight of the 11-*cis* isomer of vitamin A and an oil.

11. A composition according to claim 10, which additionally comprises a compatible anti-oxidant.

12. A composition according to claim 11, wherein the anti-oxidant is α -tocopherol acetate, *nor*-dihydroguaiaretic acid or 2,6-di-tert-butyl-4-methylphenol.

13. A composition according to any of claims 10 to 12, wherein the oil is corn oil, sesame oil or peanut oil.

14. Therapeutic compositions comprising as active ingredient the 11-*cis* isomer of vitamin A substantially as hereinbefore described.

15. Therapeutic compositions comprising as active ingredient the 11-*cis* isomer of vitamin A substantially as described in any of the specific Examples.

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